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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/052,589	01/18/2002	Dianne M. Perez	26473/04200	4045

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EXAMINER	
FALK, ANNE MARIE	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 05/19/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/052,589	PEREZ ET AL.	
	Examiner	Art Unit	
	Anne-Marie Falk, Ph.D.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *17-21* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *17-21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *02 April 2002* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The preliminary amendment filed January 18, 2002 has been entered. Claims 1-16 have been cancelled. The second preliminary amendment file April 2, 2002 has been entered. The proposed drawing change filed 4/2/02 has not been entered and is not approved for the reasons set forth below.

Claims 17-21 are pending in the instant application.

Drawings

The proposed drawing change filed 4/2/02 is not approved. First, it is noted that proposed drawing changes must be presented showing the proposed correction in **red ink.** All drawing changes must be approved by the Examiner before corrected drawings may be filed. Second, in the instant case, the change to the drawing, which involves inserting an additional nucleotide into the seuquence, constitutes new matter. At page 2 of the second preliminary amendment filed 4/2/02, Applicants state that the change to Figure 1 represents a correction of a typographical error in the nucleotide sequence. Applicants further state that they are changing the codons of the nucleotide sequence so that they are consistent with the amino acid sequence shown in Figure 1. A "T" nucleotide has been inserted at nucleotide position +506. Applicants state that the amendment corrects an obvious error and adds no new matter. The Examiner does not agree. While it is obvious that there exists an error somewhere, either in the nucleotide sequence or in the amino acid sequence, it is certainly not obvious what the correction should be. Adding an additional nucleotide to a sequence disclosure constitutes new matter. Applicants have not pointed to any support in the application as-filed for the drawing change.

Specification

The disclosure is objected to because of the following issue:

The disclosure uses the terms W1, W2, S1, T1, and T2, but does not explain what these terms mean. Thus, it is unclear what W2, S1, T1, and T2 mice are and it is impossible to determine what the specification is attempting to teach by use of these mice. See, for example, the specification at page 3, line 27, page 4, lines 5, 12, 13, 16, and 24-26, and page 17, lines 3, 4, and 5, and throughout the specification.

Appropriate correction is required.

New Matter in Specification

The amendment filed April 2, 2002 is objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. Three instances of new matter are noted. In the first instance, the added material which is not supported by the original disclosure is as follows: At page 3, line 19, the specification has been amended so that it now states that the sequence depicted in Figure 2 is the DNA sequence of the murine α_{1B} adrenergic receptor, whereas the original discloses expressly states that the sequence is the **promoter** of the murine α_{1B} adrenergic receptor. Furthermore, the specification has been amended so that it now states that the sequence depicted in Figure 2 is SEQ ID NO: 3. However, Figure 2 depicts a sequence **3498** base pairs in length, whereas SEQ ID NO: 3 is disclosed as being **3450** nucleotides in length. Thus, the sequence of Figure 2 is not SEQ ID NO: 3.

Applicant is required to cancel the new matter in the reply to this Office Action.

In the second instance, the added material which is not supported by the original disclosure is as follows: The specification has been amended so that it now includes a Sequence Listing, filed 4/2/02. SEQ ID NO: 1 is not disclosed in the specification as-filed. Figure 1 depicts a nucleotide sequence that is

2102 nucleotides in length. The sequence listing filed 4/2/02 discloses that SEQ ID NO: 1 is 2048 nucleotides in length. Thus, SEQ ID NO: 1 is not the sequence disclosed in Figure 1.

Applicant is required to cancel the new matter in the reply to this Office Action.

In the third instance, the added material which is not supported by the original disclosure is as follows: The specification has been amended so that it now includes a Sequence Listing, filed 4/2/02. SEQ ID NO: 3 is not disclosed in the specification as-filed. SEQ ID NO: 3 is disclosed as being **3450** nucleotides in length. However, Figure 2 depicts a sequence **3498** base pairs in length. Thus, SEQ ID NO: 3 is not the sequence disclosed in Figure 2.

Applicant is required to cancel the new matter in the reply to this Office Action.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Written Description

Claims 17-21 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. Applicants are referred to the final guidelines on written description published January 5, 2001 in the Federal Register at Volume 66, Number 4, pp. 1099-1111 (also available at www.uspto.gov).

Vas-Cath Inc. V. Mahurkar, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession

of the invention. The invention is, for purposes of 'written description' inquiry, whatever is claimed" (see page 1117). Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision.

The claims are directed to a method for treating a subject with a neurodegenerative disorder by administering to said subject a biologically effective amount of a compound capable of blocking activation of α_1 adrenergic receptors. Claim 18 recites that the compound is an α_{1B} adrenergic receptor (AR) antagonist. Claim 19 recites that the subject has exhibited symptoms characteristic of Parkinson's disease. Claim 20 recites that the subject has exhibited seizures. Claim 21 recites that the subject has exhibited locomotor impairment.

The Guidelines for Written Description specifically state that "[t]he claimed invention as a whole may not be adequately described if the claims require an essential or critical feature which is not adequately described in the specification and which is not conventional in the art or known to one of ordinary skill in the art" (Federal Register, Vol. 66, No. 4, page 1105, column 1). Th α_1 AR antagonists recited in the claims are an essential element of the claimed invention.

Where the claims recite "a compound capable of blocking activation of α_1 adrenergic receptors," the claims encompass the use of a large genus of compounds "capable of blocking activation of α_1 adrenergic receptors." Likewise, where the claims recite "an "α_{1B} adrenergic receptor antagonist," the claims are directed to the use of a large genus of compounds. With regard to "a compound capable of blocking activation of α_1 adrenergic receptors," the specification describes only a few compounds that would fall into this rather large genus. For example, at page 22, line 4, the specification describes the use of terazosin, an α_{1B} AR antagonist. Furthermore, the specification discloses that "the antagonists that are currently available do not have sufficient selectivity to discriminate between the subtypes" (p. 1, lines 31-32). With regard to subtypes, the specification acknowledges that there are three α_1, three α_2, and three β receptor subtypes. At page 12, lines 7-12, the specification discloses that other known α_1 AR antagonists

include phentolamine, prazosin, 5-methylurapidil, WB 4101, niguldipine, HEAT, indoramine, coryanthine, spierone, benoxathian, spiroxatrine, and chloroethylclonidined. The AR antagonists mentioned represent a diverse array of compounds, many of which are not structurally related. However, the claims cover the use of a large genus of α_1 AR antagonists, without providing guidance with regard to which antagonists would provide a receptor blockade of sufficient strength and specificity to lead to the desired treatment effect. For all intents and purposes, the claimed method is actually directed to the use of those α_1 AR antagonists that provide a receptor blockade of sufficient strength and specificity to lead to the desired treatment effect. Therefore, the claims are directed to the use of a subset of α_1 AR antagonists, for which little or no description is provided. Thus, the specification fails to describe the entire genus of α_1 AR antagonists, as recited in the claims. While the specification refers to a few α_1 AR antagonists, the specification does not teach what distinguishing features are shared by other members of this genus. In evaluating whether the written description requirement is met for genus claims, it is first determined whether a representative number of species have been described by their complete structure. In the instant case, the particular compounds mentioned in the specification would not be considered a **representative** number of species because many are not structurally related. Next then, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics. Since many of the compounds referred to in the specification are structurally diverse, and the specification does not identify a common structural element, α_1 AR antagonists have not been described by relevant identifying characteristics. This limited information is not deemed sufficient to reasonably convey to one skilled in the art that Applicants were in possession of the entire genus of α_1 AR antagonists covered by the claims, at the time the application was filed. Thus, it is concluded that the written description requirement is not satisfied for the claimed methods of using α_1 AR antagonists.

Applicants are reminded that the written description requirement is severable from the enablement requirement. *In re Barker*, 559 F.2d 588, 194 USPQ 470 (CCPA 1977), *cert.* denied, 434

U.S. 1064 (1978); *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1562, 19 USPQ2d 1111, 1115 (Fed. Cir. 1991) (While acknowledging that some of its cases concerning the written description requirement and the enablement requirement are confusing, the Federal Circuit reaffirmed that under 35 U.S.C. 112, first paragraph, the written description requirement is separate and distinct from the enablement requirement and gave an example thereof). An invention may be described without the disclosure being enabling (e.g., a chemical compound for which there is no disclosed or apparent method of making), and a disclosure could be enabling without describing the invention (e.g., a specification describing a method of making and using a paint composition made of functionally defined ingredients within broad ranges would be enabling for formulations falling within the description but would not describe any specific formulation). See *In re Armbruster*, 512 F.2d 676, 677, 185 USPQ 152, 153 (CCPA 1975).

Enablement

Claims 17-21 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, are set forth in *In re Wands*, 8 USPQ2d 1400, at 1404 (CAFC 1988). These factors include: (1) the nature of the invention, (2) the state of the prior art, (3) the relative level of skill of those in the art, (4) the predictability of the art, (5) the breadth of the claims, (6) the amount of direction or guidance presented, (7) the presence or absence of working examples, and (8) the quantity of experimentation necessary (MPEP 2164.01(a)).

The following factors have been considered.

Nature of the Invention and Scope of the Claims. The claims are directed to a method for treating a subject with a neurodegenerative disorder by administering to said subject a biologically effective amount of a compound capable of blocking activation of α_1 adrenergic receptors. Claim 18 recites that the compound is an α_{1B} adrenergic receptor (AR) antagonist. Claim 19 recites that the subject has exhibited symptoms characteristic of Parkinson's disease. Claim 20 recites that the subject has exhibited seizures. Claim 21 recites that the subject has exhibited locomotor impairment. The claims are very broad in scope, covering the treatment of any neurodegenerative disorder, including Parkinson's disease (PD), Huntington's disease, spinocerebellar ataxias (SCA), Alzheimer's disease (AD), multiple sclerosis (MS), dementia, epilepsy, ischemia, Riley-Day syndrome, globoid cell leukodystrophy, and Friedrich's ataxia, Pelizaeus-Merzbacher disease, multiple sclerosis, leukodystrophies, neuritis, and neuropathies, to name just a few. Thus, the claims cover a wide variety of neurodegenerative diseases.

The claims are also very broad in scope with regard to the compound to be administered, the mode of administration, and the region to which the compound may be administered.

Furthermore, the claims are very broad in scope with regard to the type of therapeutic effect to be achieved by the method.

Amount of direction or guidance presented and the presence or absence of working examples. The teachings of the specification are quite limited. The examples discussed in the specification are directed to transgenic mice that overexpress an α_{1B} adrenergic receptor. At page 22, lines 4-13, the specification discloses the administration of terazosin to a transgenic mouse that exhibits seizure activity. The specification discloses that fewer seizure events were observed in the mice treated with terazosin for four weeks with a daily dose of 0.05 mg/kg body weight via the drinking water. However, it is unclear what particular genetic modification is present in this mouse. Furthermore, given the limited description of the phenotype of this transgenic mouse, there appears to be little correlation to a known neurodegenerative disease, such as epilepsy, such that the mouse would be considered a model of

the disease. Thus, the specification fails to provide a working example for the treatment of a neurodegenerative disease, as art-accepted disease models are not exemplified. Furthermore, the specification does not provide a working example in a mouse model of a neurodegenerative disease, wherein the mouse is not genetically modified to overexpress the receptor that is being blocked.

Although the specification need not contain a working example if the invention is otherwise disclosed in such a manner that one skilled in the art would be able to practice it without undue experimentation, it is a factor to be considered, especially in a case involving an unpredictable art such as the therapeutic arts. See MPEP 2164.02.

State of the prior art and predictability of the art. The claims encompass a wide variety of neurodegenerative diseases. Price et al. (1998) teaches that the "neurodegenerative disorders, a heterogeneous group of chronic progressive diseases, are among the most puzzling and devastating illnesses in medicine" (abstract). See also Kumar et al. at pages 725-729 for a brief description of a few of the varied and disparate diseases that fall under the major heading of neurodegenerative disorders. The specification does not teach how a therapeutic effect would be achieved in a patient with a neurodegenerative disorder such as AD, PD, MS, or dementia.

With regard to non-protein, non-nucleic acid compound therapy, the art emphasizes the difficulty associated with developing successful treatment protocols. As discussed above, Price et al. (1998) teaches that the "neurodegenerative disorders, a heterogeneous group of chronic progressive diseases, are among the most puzzling and devastating illnesses in medicine" (abstract) and Kumar et al. (1992) discloses that "[u]nlike other categories of disease such as infections or trauma that may share etiological origins, the degenerative diseases are unified only by some general clinicopathologic features. Currently, almost all are of obscure origin, and there is no compelling reason to suppose that they have the same, or even a similar type of cause" (pages 725-726). A wide variety of therapeutic strategies for the treatment of neurodegenerative diseases are being pursued. However, despite intensive effort on the research front,

the existence of successful treatment protocols was extremely limited in May 2000, the priority date of this application.

The court has recognized that physiological activity is unpredictable. *In re Fisher*, 166 USPQ 18 (CCPA 1970). In cases involving unpredictable factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with degree of unpredictability of factors involved. *In re Fisher*, 166 USPQ 18 (CCPA 1970).

It is not to be left up to the skilled artisan to figure out how to make the necessary starting materials and then to figure out how to use them to produce the biological effects as recited in the claims. The courts held that the disclosure of an application shall inform those skilled in the art how to use applicant's claimed invention, not how to **find out** how to use it for themselves. *In re Gardner et al.* 166 USPQ 138 (CCPA 1970). This specification only teaches what is intended to be done and how it is intended to work, but does not actually teach how to do that which is intended.

Given the limited examples, the limited guidance provided in the specification, the lack of any showing of therapeutic benefit upon *in vivo* administration of a compound as recited in the claims in an art-accepted disease model, the broad scope of the claims, and the unpredictability for producing a therapeutic effect upon administration of a compound as recited in the claims, undue experimentation would have been required for one skilled in the art to develop a protocol within the scope of the claims for treating a wide variety of neurodegenerative diseases.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 17-21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 17-21 are indefinite in their recitation of "a method for treating a subject with a neurodegenerative disorder" because the preamble implies that a treatment effect will be achieved, but in fact no particular treatment effect is achieved. Thus, the preamble is in conflict with the body of the claim.

Claims 17-21 are indefinite in their recitation of "a biologically effective amount of a compound" because it is unclear what biological effect is being referred or what biological effect is desired. Thus, the metes and bounds are not clearly set forth.

Claims 17-21 are indefinite in their recitation of "capable of" because a capability is only a potential property and not an actual property. The term "capable of" implies conditionality, but the claims do not recite the conditions under which the potential property becomes an actual property. Thus, there is no requirement that activation of the named receptor is actually blocked upon administration of the compound.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne-Marie Falk whose telephone number is (571) 272-0728. The examiner can normally be reached Monday through Friday from 10:30 AM to 7:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson, can be reached on (571) 272-0804. The central official fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to Dianiece Jacobs, whose telephone number is (571) 272-0532.

Anne-Marie Falk, Ph.D.

Anne-Marie Falk

ANNE-MARIE FALK, PH.D
PRIMARY EXAMINER